

### **REMARKS**

Claims 17, 83, 95, and 96 are under consideration in this case, and were finally rejected in the previous Office Action, issued November 7, 2008. No changes to the claims are made at this time. In view of the arguments and remarks set forth below, Applicant's respectfully request reconsideration of the final rejection in the last Office Action.

#### **Information Disclosure Statements**

A review of the file shows that Information Disclosure Statements on Forms 1449 filed July 28, 2008, February 3, 2006, December 28, 2004, and September 13, 2004 were not signed by the Examiner. The Form 1449 filed July 21, 2004 was signed by the Examiner on June 6, 2005.

Applicants respectfully request that the Examiner review the above noted Forms 1449 and sign them for the record.

#### **Claim Rejections**

In the Office Action, claims 17, 83, 95, and 96 were rejected as obvious, because amorphous valsartan was allegedly in the prior art. Applicants respectfully traverse this rejection.

The Applicants previously submitted a declaration from inventor Tamas Koltai, stating the claimed invention is distinct from the prior art. However, the Office Action asserts that "the declaration does not show that the instant amorphous form is not found in the prior art. Rather, the declaration seems to indicate that the amorphous form is present in the prior art." Applicants respectfully disagree. Applicants assert that amorphous valsartan is not in the prior art. The prior art form of valsartan from the Marti et al, in WO 02/06253 and Bühlmayer (U.S. 5,399,578) is in fact a partly amorphous material contaminated with a considerable amount of crystallinity. That is evidenced by the Koltai declaration.

The Marti publication (bottom page 1-top page 2) states that the valsartan (free acid) with a melting enthalpy of 12 kJ/mol is “almost amorphous,” and has a “considerable residual arrangement,” i.e., a considerable degree of crystallinity. The crystalline contamination is evidenced by the data provided in the declaration of Tomas Koltai in this case, filed July 20, 2008.

Our position is further supported by the declaration of Prof. Guatam Desiraju submitted herewith. Prof. Desiraju is an expert in polymorphism and solid state forms of materials. In the Desiraju declaration, paragraph 10 notes that the prior art valsartan discussed in Marti at pages 1-2 has “a substantial amount of order,” and “at best [is] an impure amorphous material.”

Additionally, the claims of the instant application recite a melting enthalpy of less than about 1 J/g. By contrast, as noted in the Koltai and Desiraju declarations, the prior art valsartan has a melting enthalpy of about 28 J/g (corresponding to 12 kJ/mol). Furthermore, Prof. Desiraju makes clear (in para. 11) that the instant application has no measurable melting enthalpy at all, based on the data of Fig. 3 of the present application, of the DSC of the pure amorphous valsartan of the present claims, which shows no detectable melting enthalpy. Thus, the prior art valsartan has greater than a 28-fold more melting enthalpy than the claimed valsartan.

The Marti publication acknowledges that the “almost amorphous” prior art valsartan is disadvantageous. The invention in the Marti publication solves the problem of impure solid state forms of valsartan by preparing metal salts, which are asserted to be more crystalline than the free acid.

Thus, the prior art “almost amorphous” valsartan was not purely amorphous; nor was the prior art material intended to be a relatively pure amorphous valsartan. The presence of non-crystalline valsartan in the prior was taken to be a disadvantage. Accordingly, Marti teaches away from the utility of amorphous valsartan, and evinces no intent to prepare amorphous valsartan.

The Office Action asserted that Applicants' admit that amorphous valsartan is in the prior art, and that "something old does not become patentable on discovery of a new property or inherent feature." Applicants respectfully disagree with this conclusion. The prior art valsartan from Marti and Bühlmayer is only partially amorphous, and as noted above, is contaminated with substantial amounts of crystalline material. Thus, pure amorphous valsartan is not "something old." By contrast, the instant inventors have found methods to prepare highly pure amorphous valsartan that was not known or suggested by the prior art.

Applicants respectfully submit that the purely amorphous material of the instant invention is patentable. "A purified compound is not always *prima facie* obvious over the mixture; for example, it may not be known that the purified compound is present in or an active ingredient of the mixture, or the state of the art may be such that discovering how to perform the purification is an invention of patentable weight in itself." *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1301 (Fed. Cir. 2007).

Here, Prof. Desiraju concludes that the purely amorphous material of the instant invention is substantially different than that provided in the prior art (para. 9). Prof. Desiraju further distinguishes the desirability of polymorphically pure substances, particularly the advantages of a purely amorphous substance (para. 14). Prof. Desiraju also notes the unpredictability of preparing a pure amorphous substance by conventional purification techniques absent considerable experimentation (para. 15).

### **Conclusion**

For the foregoing reasons, the Applicants respectfully submit that the claims of the instant application are novel, nonobvious, and patentably distinct over the prior art Marti and Bühlmayer documents. Applicants therefore respectfully urge that the instant claims are in condition for allowance.

Respectfully submitted,

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